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Functional and cognitive outcomes in patients with covert cognition during acute intensive rehabilitation

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ABSTRACT

Background: Disorders of consciousness (DOC) result from focal or extensive brain lesions. Patients suffering from DOC go through neurobehavioral assessments and are classified in different categories: coma, unresponsive wakefulness syndrome (UWS) (also known as vegetative state) and minimally conscious state (MCS). Recently, the broader use of technologies, such as functional neuroimaging and electroencephalography, has allowed the highlighting of preserved cognitive capacities in patients behaviourally categorized as UWS or MCS. Such condition is called cognitive motor dissociation (CMD).

Objectives: 1) To investigate the consciousness/functional recovery in patients with disorders of consciousness (DOC) as well as those presenting with cognitive motor dissociation (CMD), 2) to compare the different functional outcomes to see whether those with preserved cognitive capacities differ and 3) to evaluate the patients' clinical evolution between admission and discharge.

Method: We retrospectively included 141 patients admitted to the Acute Neuro-rehabilitation Unit (NRA) of the University Hospital of Lausanne (CHUV, Lausanne, Switzerland) from November 2011 to August 2018 and investigated their functional outcomes at admission and discharge using 6 different outcome scales. Univariate analyses were then performed to compare the different functional outcomes.

Results: Patients presenting with CMD were significantly associated with better functional outcomes and potential of improvement than the patients suffering from DOC.

Conclusion: Our findings support the fact that CMD patients constitute a separate category of patients with different potential of improvement and functional outcomes than patients suffering from DOC. This reinforces the need for them to be recognized as soon as possible, as it could have a direct impact on patient care and influence life and death decisions.

KEYWORDS

Disorders of consciousness; cognitive motor dissociation; covert cognition; functional outcomes; early rehabilitation

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INTRODUCTION

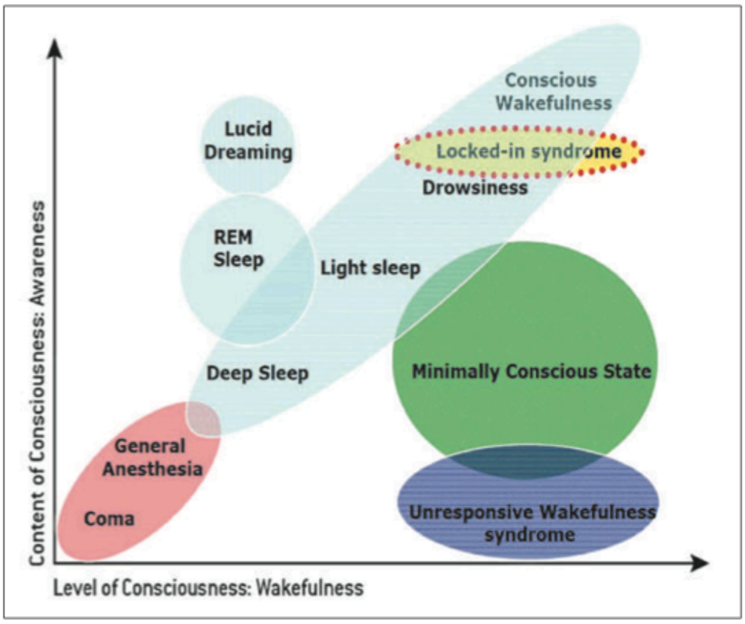
Consciousness is very often a difficult concept to explain, as it has more to do with something experienced than described. According to James (1), "at its least, normal human consciousness consists of a serially time-ordered, organized, restricted and reflective awareness of self and the environment. Moreover, it is an experience of graded complexity and quantity." For Plum and Posner (2), "Consciousness means awareness of self and environment". Furthermore, it can be defined as the ability to self-report. Being conscious is therefore a personal and internal process of recognising something as a conscious content (3-4).

Usually described as a bidimensional model, consciousness is characterized by two major components: arousal and awareness (5).

Arousal, also called wakefulness, refers to the level of consciousness (6). It goes from deep dreamless sleep to alert wakefulness and is controlled by the ascending reticular activating system (ARAS) (5). ARAS is a dense neuronal network originating from the upper brainstem and projecting to the cortex via the thalamus. It promotes arousal by facilitating the passage of sensory information to the brain.

Awareness refers to the content of consciousness (6). The latter consists of an individual's subjective experience and is influenced by many aspects, such as sensations, emotions, thoughts, imagination etc. (5). In order to have a conscious perception, stimuli must be transmitted to the primary cortices, the secondary cortices (higher-order areas) and to the frontoparietal network, a functional integrating region encompassing polymodal associative cortices and connected to the thalamus (via cortico-thalamo-cortico pathways) (7). For example, an auditory stimulus that triggers an activation of primary auditory cortices won't be consciously perceived if not transmitted to higher-order multimodal areas (secondary and associative cortices)(8). Thus, cerebral activation limited to subcortical areas and primary cortices is not sufficient for awareness because of its need for higher-order integration.

*Figure 1: Illustration of the two major components of consciousness: arousal (wakefulness) and awareness **



**Taken from (9), originally adapted from (7)*

Disorders of consciousness (DOC)

Disorders of consciousness (DOC) result from focal or extensive brain lesions that, following a period of coma/complete loss of consciousness, induce an alteration in arousal and/or awareness, hence preventing patients to interact with their environment. Aetiologies of DOC are multiple and various, but can be classified in two major categories: traumatic versus non-traumatic brain injuries. Traumatic brain injuries include falls, acceleration/deceleration injuries, violence, penetrating injuries, etc. whereas non-traumatic injuries mainly consist of hypoxic injuries, non-traumatic haemorrhages, tumours, metabolic disorders, infectious diseases or toxic exposure.

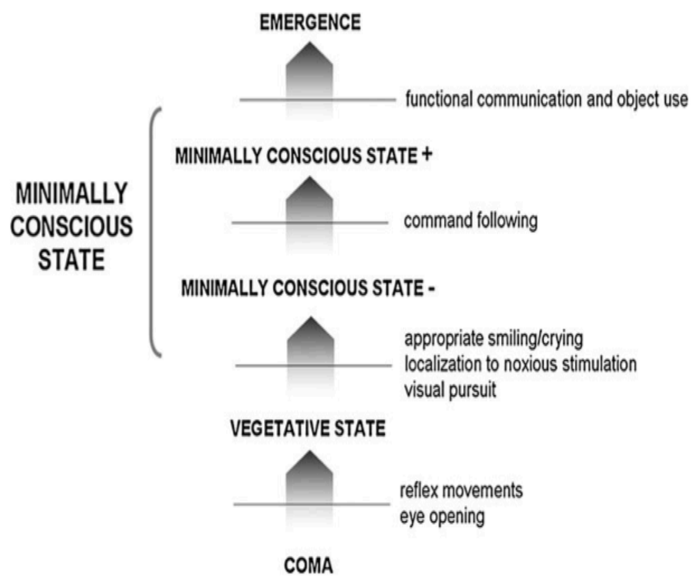
The incidence of traumatic brain injury in the United States is estimated to be between 180 and 250 per 100'000 population per year (10). A systematic review in Europe reported the incidence to be between 47.3 and 846 per 100'000 population per year (11). In Switzerland, a cohort study revealed an incidence of severe traumatic brain injury of 8.2 per 100'000 person-years (12). Because of the improvement in the management of patients suffering from severe brain injuries, the number of patients surviving those types of injuries has increased in the recent years. According to a study conducted by Siman-Tov *and al.* (13) in all level 1 trauma centres in Israel, the mortality associated with traumatic brain injury has decreased from 17% in 2000 to 11% in 2010. However, approximately 20% of the patients who survive from a brain injury will suffer from a disorder of consciousness (14).

Coma is an acute disorder of consciousness where the patients remain unresponsive to any stimulation, show no sign of awareness nor wakefulness with the eyes constantly closed and a loss of sleep-wake cycle (15).

Patients who survive coma will usually evolve into a state described as the *unresponsive wakefulness syndrome* (UWS), also known as the *vegetative state* (VS). UWS patients show signs of wakefulness, with the alternation of eyes open and closed as well as a remaining pattern (although pathological) of sleep-wake cycles. However, they stay unresponsive. Indeed, no behavioural awareness can be highlighted in such patients (15-16).

The *minimally conscious state* (MCS), a state in which patients can evolve from UWS, is characterized by the presence of different levels of transitory awareness. Just like the UWS patients, MCS patients show signs of wakefulness but they also demonstrate inconsistent but not reflexive behavioural evidence of self or environment awareness (17). Furthermore, Bruno *and al.* (18) proposed a sub-categorization into MCS- and MCS+. MCS- (low-end behaviours) includes visual pursuit and localization of noxious stimulation whereas MCS+ (high-end behaviours) includes command following, comprehensible verbalizations and/or non-functional communication. Those two categories not only differ in term of behaviours, they also show a different functional neuroanatomy (see below).

Figure 2*: Clinical criteria of disorders of consciousness**



**Taken from (18)*

Table 1*: Characteristic clinical features of coma, unresponsive wakefulness syndrome and minimally conscious state**

	Coma	UWS	MCS
Wakefulness	No sleep-wake cycles Eyes closed	Intermittent periods of wakefulness manifested by the presence of sleep/ wake cycles (i.e., periodic eye opening)	Intermittent periods of wakefulness
Awareness	No behavioural sign of self-awareness or environmental awareness	No behavioural sign of self-awareness or environmental awareness	Inconsistent but clear-cut behavioural signs of self-awareness or environmental awareness
Receptive language	None	None	Inconsistent one-step command following gestural or verbal "yes/no" responses (regardless of accuracy)
Expressive language	None	None	Not spontaneous and limited to single words or short phrases, yet intelligible
Visual perception	None	Inconsistent visual startle No sustained fixation nor pursuit	Visual pursuit Object recognition
Motor function	Primitive reflexes only	Gradual resumption of spontaneous or elicited movement, however always non-purposeful or reflexive	Purposeful behaviours including movements or affective behaviours in contingent relation to relevant stimuli Localisation to noxious stimuli Object manipulation Automatic movement sequences

** Reproduced from (9), originally adapted from (19)*

Functional neuroanatomy of UWS and MCS

Using 18-fluorodesoxyglucose positron emission tomography, Laureys *and al.* (20-21-22) described the central role of the frontoparietal network's connectivity and his thalamic connections in the maintenance of awareness. Indeed, UWS patients presented a significant dysfunction in the associative areas of the prefrontal, premotor and parieto-temporal cortices while MCS patients showed only a partial impairment of those networks. Furthermore, disconnections between the primary sensory areas and the higher-order associative cortices have been highlighted in UWS patients (23-24) whereas MCS patients demonstrate a more elaborated and integrated level of processing (25-26), thus supporting the importance of those connections for conscious perceptions. Moreover, as discussed above, the sub-categorizations MCS- and MCS+ proposed by Bruno *and al.* (18) demonstrated different neuroanatomy. Indeed, MCS- showed a preserved right hemispheric cortical metabolism (more likely indicating residual sensory consciousness) with impaired left cortical networks, whereas MCS+ showed a preserved metabolism and functional connectivity in language networks. Those findings join the results of Rodriguez Moreno *and al*. (27) in their fMRI study of DOC patients suggesting that the activity of the language network could be an indicator of higher-level cognition.

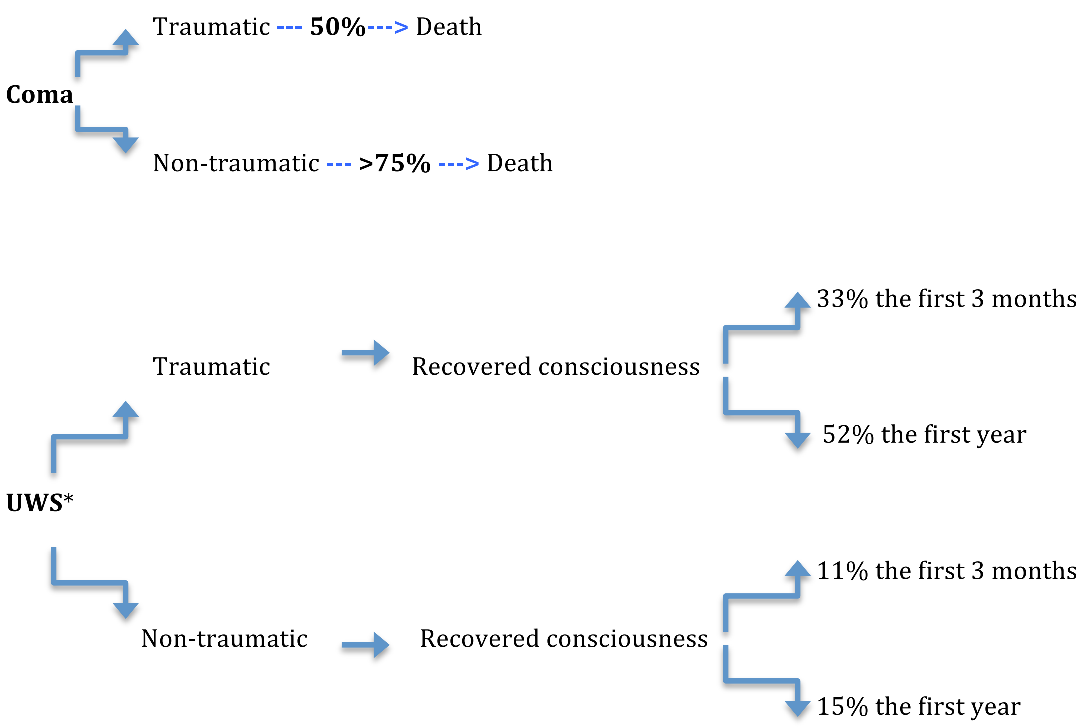
Cognitive motor dissociation (CMD)

Recently, the broader use of technologies, such as functional neuroimaging and electroencephalography, has brought new insights into the understanding of DOC. A major input was the highlighting of preserved cognitive capacities in patients with no behavioural sign. Indeed, in their study Owen *and al.* (28) gave a patient, clinically diagnosed in VS five months post injury, spoken instructions to perform mental imagery tasks (playing tennis and visiting the rooms of her house). Her neural responses measured through fMRI were indistinguishable from those observed in healthy volunteers, demonstrating her preserved ability to understand spoken commands and respond to them through her brain activity. This confirmed that despite her inability to express it through speech or movement, the patient was consciously aware of herself and her surroundings. Goldfine *and al.* (29) demonstrated that awareness could also be detected by EEG power spectral analysis in chronic patients showing no behavioural sign. Similar results were found by Monti *and al.* (30), confirming the existence of patients who show limited or no sign of consciousness at bedside but, when using functional technologies, prove to have residual cognitive functions and even conscious awareness. Edlow *and al.* (31) demonstrated that covert consciousness can not only be present in patients suffering from chronic disorders of consciousness, but it can also be highlighted in patients during the acute phase of a brain injury, hence the importance to detect those patients already in the intensive care units (ICU). Schiff (32) proposed the term *cognitive motor dissociation* (CMD) to define such patients. The underlying mechanisms associated with this condition are not fully understood yet. In the study by Fernandez-Espejo *and al.* (33), CMD patients demonstrated a selective bilateral interruption in the white matter connections between the thalamus and the motor cortex, thus inhibiting the excitatory coupling necessary for the motor execution. Nevertheless, CMD patients seem to have a preserved high cerebral integrity (34). Because of the lack of behavioural signs, CMD patients are often wrongly clinically classified as coma, UWS or MCS-. According to a systematic review and meta-analysis conducted by Kondziella *and al.* (35), approximately 15% of the patients clinically diagnosed with UWS demonstrate preserved command following.

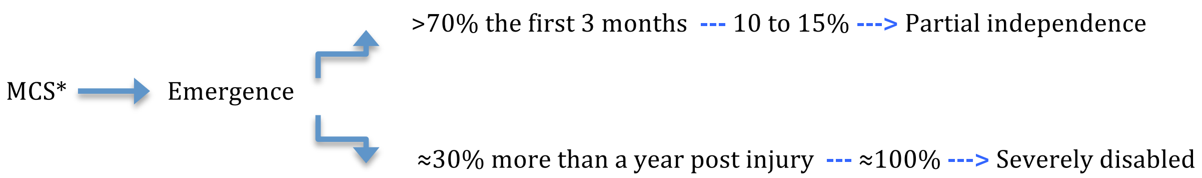
DOC outcomes

Having an accurate diagnosis is essential to direct patients' management and predict the outcome of their condition. Indeed, approximately 50 % of patients suffering from a post-traumatic coma will die (36). Less than 25 % of patients suffering from a non-traumatic coma will survive the first month (37). Patients that recover from coma will usually go through the UWS and MCS states. Thirty-three % of UWS patients with post-traumatic brain injury regain consciousness within the first three months. One year post injury, recovered consciousness can be seen in 52% of the patients. Only 11% of patients in UWS post non-traumatic brain injury recovered consciousness after three months and 15% after a year (38). More than 70% of patients emerge from MCS during the first three months after coma onset (39). Ten to 50% of them will at least recover partial independence for the activities of the daily living and the locomotion after a year (39-40-41-42). Approximately 30% of patients will emerge from MCS more than one year post injury, however with severe or complete disabilities (43). As for the CMD patients, to our knowledge, no data concerning their outcome is yet reported.

***Figure 3**: Schematic representation of the DOC outcomes*



**Unresponsive wakefulness syndrome*



**Minimally conscious state*

Neurobehavioural assessment

The *JFK Coma Recovery Scale-Revised* (CRS-R) (44) is used as a standard for assessing the patients' level of consciousness and establishing a diagnosis. In a systematic review of 13 behavioural assessment scales conducted by Seel *and al.* (45), the CRS-R received the strongest recommendation. It proved to have an excellent content validity and was the only scale addressing all the Aspen workgroup criteria (17). Nevertheless, the rate of misdiagnosis is as high as 43% (46-47). Indeed, it remains challenging to perform an accurate evaluation. The clinical assessment can be influenced by many different factors regarding the patients themselves (variability in the patients' response due to arousal fluctuations, pain, associated illnesses, etc.) or their environment (medication, position, noise, light, etc.). It can also suffer from a certain variability due to the subjective bias of the observer (examiner dependant).

The fact that the CRS-R quotation depends on stringent criteria, with notably the need for the patients to repetitively show clear behavioural signs by responding to verbal and neurosensory stimulations through motor outputs, may lead to a clinical underestimation of the level of consciousness and more so of its content, in cases of aphasia or blocked motor efferences (see full CRS-R in *appendix A*).

Table 2*: CRS-R items**

Items	**Scores**
Auditory function scale	0- None, 1- Auditory startle, 2- Localization to sound, 3- Reproducible movement to command, 4- Consistent movement to command
Visual function scale	0- None, 1- Visual startle, 2- Fixation, 3- Visual pursuit, 4- Object localization, 5- Object recognition
Motor function scale	0- None/flaccid, 1- Abnormal posturing, 2- Flexion withdrawal, 3- Localization to noxious stimulation, 4- Object manipulation, 5- Automatic motor response, 6- Functional object use
Oromotor/verbal function scale	0- None, 1- Oral reflexive movement, 2- Vocalization/oral movement, 3- Intelligible verbalization
Communication scale	0- None, 1- Non-functional, 2- Functional
Arousal scale	0- Unarousable, 1- Eye opening with stimulation, 2- Eye opening without stimulation, 3- Attention

** Based on (48)*

Other scales can be used for the neurobehavioural assessment of patients with DOC. For example, the *Glasgow Coma Scale* (GCS) represents a simple and practical method to assess the level of consciousness by measuring three categories of responsiveness: the eye opening, the motor and verbal responses (49). Well-established and widely used, some authors have however raised concerns about the inconsistency and confusion in its use (50) and therefore its lack of reliability. Furthermore, in their 10 years data report of brain injured patients, Balestreri *and al.* (51) showed a reduction in the GCS predictive value for outcome.

The *Wessex Head Injury Matrix* (WHIM) is a 62 items hierarchical scale reflecting the order of recovery for patients emerging from coma (52). Its items regard basic behaviours, social aspects, communication, attention, cognitive capacities, memory and orientation. Originally designed to monitor patients' recovery, it is also used as an assessment scale for DOC. According to the systematic review from Seel *and al*. (45), it demonstrates a good content validity, with items allowing the distinction between VS and MCS, and an acceptable standardized administration. On the other hand, it showed a lack of inter-rater reliability and criterion validity. It can therefore be used to assess DOC with moderate reservations.

The *Sensory Modality Assessment Technique* (SMART) is a scale consisting in 8 modalities. It evaluates the response to visual, tactile, auditory and olfactory stimuli as well as the level of arousal, the motor function and the ability to communicate (53). According to the systematic review from Seel *and al.* (45), it demonstrates a good content validity with items allowing the distinction between VS and MCS and acceptable standardized administration/scoring procedures. However, it showed limited evidence of reliability and criterion validity. It can be used to assess DOC with moderate reservations.

In a study from the Acute Neurorehabilitation Unit (CHUV, Lausanne), the use of a Complementary Motor Behavioural Tool in association with the CRS-R has demonstrated an improvement in diagnosis and outcome predictability (54) of such patients described as CMD. Recently, a revised and simplified version of it, the MBT-r, has been validated as a stand-alone form (55) (see full MBT-r in *appendix B*). By allowing the detection of subtle behavioural signs, the MBT-r uncovers evidences of residual cognition in patients considered unconscious (coma/UWS). The fact that CMD patients fail to evoke proper motor responses at bedside testifies more for an impairment in the efferent pathways rather than for a true disorder of consciousness.

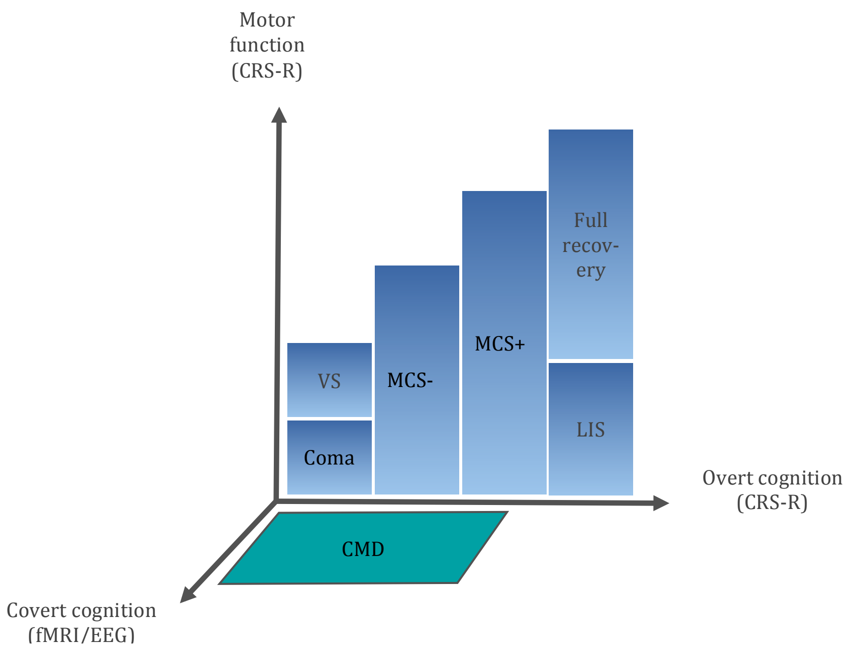
Table 3: *MBT-r items**

Items
Positive signs
1. Spontaneous non-reflexive movements
2. Response to command
3. Visual fixation or visual pursuit
4. Motor responses in a motivational context
5. Responses to noxious stimulation
Negative signs
6. Abnormal posturing or neurovegetative responses to stimulation
7. Signs of roving eyes or absence of oculocephalic reflex

**Based on (55)*

Because CMD patients demonstrate preserved cognitive capacities, it is essential for them to be distinguished from the DOC patients, as their outcome could potentially be different.

Figure 4: *Schematic of the three dimensions of detecting consciousness**



Legends: VS: vegetative state, MCS-: minimally conscious state without language function; MCS+: minimally conscious state with language function; CMD: cognitive motor dissociation; LIS: locked-in syndrome
**Adapted from (31)*

In this study, we will therefore 1) investigate the consciousness/functional recovery in patients with disorders of consciousness (DOC) as well as those presenting with CMD, 2) compare the different functional outcomes to see whether the outcomes of those with preserved cognition differ and 3) evaluate the patients' clinical evolution between admission and discharge.

We hypothesize that the functional outcomes of the CMD patients will differ from those with DOC. Furthermore, because of their preserved cognition, we expect CMD patients to present a better potential of improvement and therefore, better outcomes than the DOC patients.

METHODOLOGY

Participants

We retrospectively enrolled the 145 patients that have been admitted to the Acute Neurorehabilitation Unit (NRA) of the University Hospital of Lausanne (CHUV, Lausanne, Switzerland) from November 2011 to August 2018.

In order to be included, patients had to be 1) at least 16 years old, 2) suffering from a severe acquired brain injury requiring an intermediate care structure and 3) receiving an Early Rehabilitation Barthel Index (ERBI) score <30.

The exclusion criteria were any co-existent non-neurological disorders, neuromuscular disturbances and/or diseases involving peripheral nervous system (critical illness polyneuropathy, spinal muscular atrophy, Guillain-Barré Syndrome).

Among the 145 patients enrolled, 4 were excluded.

The 141 patients included suffered from traumatic and non-traumatic brain injuries. Traumatic brain injuries (TBI) include motor vehicle collisions, falls and assaults, whereas non-traumatic brain injuries (NTBI) consist of vascular injuries, anoxia, encephalopathies and neoplasms.

Procedure

Patients' neurobehavioural assessment was performed in the ICU, before their admission in the NRA unit, using the CRS-R and the MBT-r. The patients were then separated in 3 categories according to their diagnosis: CMD, DOC and NON-DOC (patients with no pathological interaction when stimulated after withdrawal of sedation, considered as controls).

All the patients underwent a clinical and neurological evaluation at both admission and discharge from the NRA unit.

During their stay, they benefited from an individualized intensive (at least 3 hours a day, 5 days a week) rehabilitation program, which included physical, occupational, neuropsychological and speech therapies.

Functional outcomes were investigated at their admission and discharge using the following outcome scales (full outcomes scales can be found in *appendix C*):

The Glasgow Outcome scale (GOS) (56): was first published in 1975 by Jennett and Bond (57) in an effort to objectively assess the outcome of the increasing survivors of brain injuries. Initially designed to assess the patients' outcomes in community, it can be used in both in acute and chronic settings (58). Since its publication, it has been widely recognised as a simple, reliable and valid outcome measure. It consists in five descriptive categories (dead; vegetative; severely disabled; moderately disabled; good recovery) and is often separated in two: favourable (moderately disabled; good recovery) versus unfavourable outcomes (dead; vegetative; severely disabled).

The Early Rehabilitation Barthel Index (ERBI) (59): an extended version of the Barthel index (60) (which is focusing more on the daily activities) providing a better assessment of patients in early rehabilitation, as it contains items concerning tracheostomy, mechanical ventilation and dysphagia. The scoring of ERBI is separated in 4 categories. A score between -75 and 30 or >30 is considered a good outcome, whereas a score <-200 or between -200 and -76 is considered a poor outcome.

The Disability Rating Scale (DRS) (61): designed to assess disability after brain injury and to follow the progress during recovery, it can therefore be administrated in a large variety of settings from the acute care units to community (62). It evaluates eight sub-categories (eye opening, communication ability, motor response, feeding, toileting, grooming, level of functioning and employability) and a score ≤ 11 is considered a good outcome.

The Rancho Los Amigos Levels of Cognitive Functioning (LCF) (63): initially developed to assess patients emerging from coma, it can follow the cognitive and behavioural recovery of patients with brain injury. Often paired with the Glasgow Coma Scale (GCS) for the initial assessment of patients suffering from brain injury, its use is however not limited to the acute phase. It consists in ten categories going from total assistance to independence. Patients classified from the 6th category up to the 10th are considered having a good outcome.

The modified Rankin Scale (mRS) (64-65): widely used to evaluate patients after a stroke, it assesses the degree of global disability and dependence. The scoring goes from 0 (no symptom) to 6 (death). A score ≤3 is considered a good outcome.

The Functional Ambulation Classification Scale (FAC) (66): evaluates the functional walking capacity with a score from 0 to 6 and offers an easier alternative to the measurement of the walking velocity. A score ≥2 is considered a good outcome.

Protocol approval and patients' consent

The protocol of this study has been approved by the Ethics Committee of Lausanne (142-09).

The patients' legal representatives were informed and gave a written consent.

Statistics

We first analysed our data using descriptive statistics to observe the general distribution of the variables and to detect any extreme values (outliers).

We then performed univariate analysis. In order to determine if the variables' distribution differed from one group to another, we compared them two by two using Student's t-test. Results were considered significant for a p-value < 0.05.

Because certain variables took only a limited amount of values, we analysed the distribution differences between the different groups using Fischer test.

We also investigate the sensitivity and specificity of the prediction of consciousness recovery according to the CRS-R. We considered as true positive outcome the patients classified as CMD (as opposed to DOC). Intervals of confidence (CI) were computed using the Wilson method.

RESULTS

Among the 141 patients included, 105 were diagnosed as CMD (74.47%), 19 as DOC (13.47%) and 17 as NON-DOC (12.06%). In the CMD category, 39 were female (37.14%) and 66 male (62.86%). The patients' age varied from 17 to 83 years old. Forty (38.10%) suffered from traumatic brain injury and 65 (61.90%) from non-traumatic brain injury. The length of their hospitalization in the NRA unit varied from 7 to 77 days. Concerning their diagnosis according to the CRS-R, 21 were diagnosed in coma, 39 in UWS, 1 in UWS/MCS and 44 in MCS. In the DOC patients' category, 11 were female (57.89%) and 8 (42.11%) male, aged from 17 to 75 years old. Eleven (57.89%) of them suffered from a traumatic brain injury whereas the other 8 (42.11%) suffered from a non-traumatic brain injury. Their stay in the NRA unit varied from 8 to 41 days. Concerning the NON-DOC patients, 4 were female (23.53%) and 13 were male (76.47%), aged from 24 to 78 years old. Three (17.65%) suffered from a traumatic brain injury and 14 (82.35%) from a non-traumatic brain injury, with a length of stay varying from 7 to 46 days.

Table 4: *Summary of the demographic and clinical information*

	CMD patients	DOC patients	NON-DOC patients
Number	105	19	17
Sex F/M (n)	39/66	11/8	4/13
Age (years)	From 17 to 83	From 17 to 75	From 24 to 78
Aetiology TBI/NTBI (n)	40/65	11/8	3/14
Length of stay (days)	From 7 to 77	From 8 to 41	From 7 to 46

Abbreviations: TBI: traumatic brain injury; NTBI: non-traumatic brain injury

The Glasgow Outcome Scale (GOS)

At admission, the scoring of the GOS took only two different values. Fourteen of the CMD patients (13.33%) and 15 of the DOC patients (78.95%) received a score of 2, whereas 91 of the CMD patients (86.67%), 4 of the DOC patients (21.05%) and the 17 NON-DOC patients (100%) received a score of 3. Lower scores were observed for the DOC patients than for the CMD and NON-DOC ones and Fischer's exact test for differences in distribution was significant (p-value<0.001 in both cases). Fischer's exact test for differences in distribution between the CMD and NON-DOC patients was not significant (p-value=0.214).

At discharge, 3 of the CMD patients (2.85%), 1 of the DOC patients (5.26%) and 1 of the NON-DOC patients (5.88%) received a score of 1. Three (2.85%) of the CMD and 8 (42.11%) of the DOC patients received a score of 2. Sixty-five (61.91%) of the CMD, 10 (52.63%) of the DOC and 8 (47.06%) of the NON-DOC patients received a score of 3. Twenty-seven (25.72%) of the CMD and 5 (29.41%) of the DOC patients received a score of 4. Seven (6.67%) of CMD and 3 (17.65%) of the NON-DOC patients received a score of 5. None of the DOC patients evolved enough to meet those higher scores. Lower scores were observed for the DOC patients than for the CMD and NON-DOC ones and Fischer's exact test for differences in distribution was significant (p-value<0.001 in both cases). Fischer's exact test for differences in distribution between the CMD and NON-DOC patients was not significant (p-value=0.214).

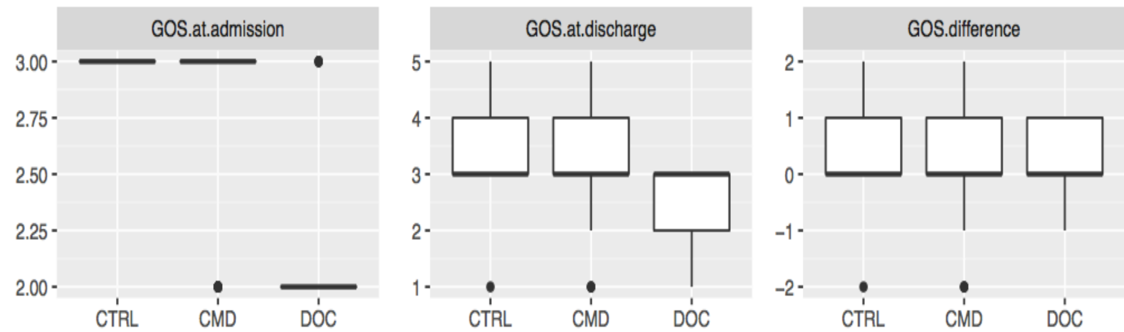
During their hospitalization, 5 (4.77%) of the CMD, 1 (5.26%) of the DOC and 1 (5.88%) of the NON-DOC patients lowered their score from 1 or 2 points. The scoring remained the same for 53 (50.48%) of the CMD, 12 (63.16%) of the DOC and 8 (47.06%) of the NON-DOC patients. Forty-seven (44.75%) of the CMD, 6 (31.58%) of the DOC and 8 (47.06%) of the NON-DOC patients improved their score from 1 or 2 points. Fischer's exact test for differences in distribution was not significant (CMD vs. DOC, p-value=0.535; CMD vs. NON-DOC, p-value=0.403; DOC vs. NON-DOC, p-value=0.195).

Table 5: *Summary of the GOS results*

Variable	Value	CMD n.	DOC n.	NON-DOC n.	CMD prop.	DOC prop.	NON-DOC prop.
GOS at admission	2	14	15	0	0.13333	0.78947	0
	3	91	4	17	0.86667	0.21043	1
GOS at discharge	1	3	1	1	0.02857	0.05263	0.05882
	2	3	8	0	0.02857	0.42105	0
	3	65	10	8	0.61905	0.52632	0.47059
	4	27	0	5	0.25714	0	0.29412
	5	7	0	3	0.06667	0	0.17647
GOS difference	-2	3	0	1	0.02857	0	0.05882
	-1	2	1	0	0.01905	0.05263	0
	0	53	12	8	0.50476	0.63158	0.47059
	1	40	6	5	0.38095	0.31579	0.29412
	2	7	0	3	0.06667	0	0.17647

Abbreviations: n: number; prop: proportion

Table 6*: Boxplots of the GOS distribution*



The Early Rehabilitation Barthel Index (ERBI)

The mean ± standard deviation (SD) of the scores at admission was -248.48 ± 69.97 for the CMD patients, -289.48 ± 36.63 for the DOC patients and -185.89 ± 99.29 for the NON-DOC patients. The variables' distribution significantly differed between the 3 categories (Student's t-test: CMD vs. DOC, p-value<0.001; CDM vs. NON-DOC, p-value=0.022; DOC vs. NON-DOC, p-value<0.001).

At discharge, the mean of the scores was -19.20 ± 108.99 for the CDM patients, -222.27 ± 92.19 for the DOC patients and 16.48 ± 81.14 for the NON-DOC patients. Student's t-test attested a significant difference in distribution between the DOC category and both the CMD and NON-DOC categories, with a p-value<0.001. No significant difference was found between the CMD and NON-DOC categories (Student's t-test, p-value=0.123)

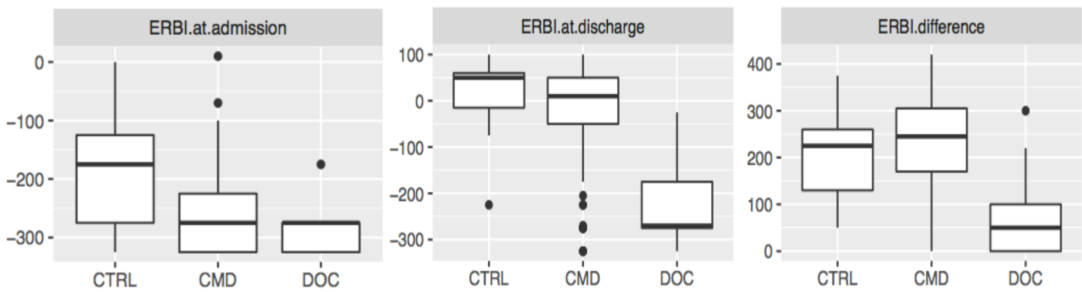
CMD and NON-DOC patients improved significantly more their score during their hospitalization when compared to the DOC patients, with a mean's difference of 229.29 ± 108.68 and 202.36 ± 92.57 versus 66.85 ± 86.47 (Student's t-test, p-value<0.001). No significant difference regarding the scores' improvement between the CMD and NON-DOC patients was found (Student's t-test, p-value=0.289).

Table 7: *Detailed ERBI distribution*

Variable	GRP	Ndiffval	Mean	SD	Median	IQR	Min	Max
ERBI at admission	CMD	11	-248.476	69.9695	-275	100	-325	10
	DOC	4	-289.474	36.6248	-275	50	-325	-175
	NON-DOC	10	-185.882	99.2824	-175	150	-325	0
ERBI at discharge	CMD	44	-19.1905	108.984	10	100	-325	100
	DOC	10	-222.632	92.1859	-270	100	-325	-25
	NON-DOC	15	16.4706	81.1396	50	75	-225	100
ERBI difference	CMD	51	229.286	108.673	245	135	0	420
	DOC	8	66.8421	86.4615	50	100	0	300
	NON-DOC	17	202.353	92.5695	225	130	50	375

Abbreviations: GRP: group; Ndiffval: number of different values; SD: standard-deviation; IQR: interquartile range

Table 8: *Boxplots of the ERBI distribution*



The Disability Rating Scale (DRS)

The scores' distribution at admission was significantly different between the 3 categories (Student's t-test, p-value<0.001 for each comparison: CMD vs. DOC, CDM vs. NON-DOC and DOC vs. NON-DOC). The NON-DOC patients globally received lower scores (16.30 ± 4.67) than the CMD patients (21.55 ± 3.33) and the DOC patients (24.95 ± 2.18).

The difference persisted at discharge with, according to Student's t-test, a p-value<0.001 when comparing CMD vs. DOC and DOC vs. NON-DOC, and a p-value=0.004 when comparing CDM vs. NON-DOC. The scores remain lower for the NON-DOC patients (6.77

± 4.43) when compared to the CMD (10.75 ± 6.70) and DOC patients (22.85 ± 4.01).

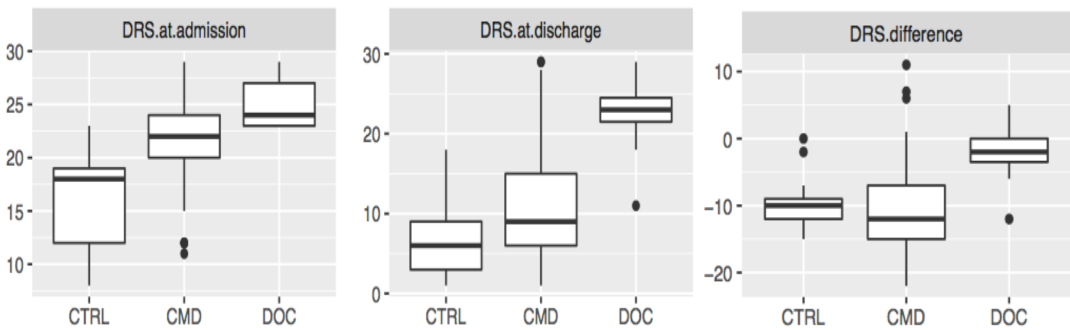
During their stay, the CMD and NON-DOC patients lowered significantly more their score (-10.80 ± 6.29 and -9.53 ± 3.94 respectively) than the DOC patients (-2.11 ± 3.50) with in both comparisons a p-value <0.001 according to the Student's t-test. The evolution of the scores of the CMD and NON-DOC patients was not significantly different (Student's t-test, p-value=0.272).

Table 9: *Detailed DRS distribution*

Variable	GRP	Ndiffval	Mean	SD	Median	IQR	Min	Max
DRS at admission	CMD	17	21.5429	3.3225	22	4	11	29
	DOC	6	24.9474	2.17239	24	4	23	29
	NON-DOC	11	16.2941	4.66054	18	7	8	23
DRS at discharge	CMD	26	10.7429	6.6982	9	9	1	29
	DOC	11	22.8421	4.00365	23	3	11	29
	NON-DOC	11	6.76471	4.42337	6	6	1	18
DRS difference	CMD	27	-10.8	6.28092	-12	8	-22	11
	DOC	10	-2.10526	3.49436	-2	3.5	-12	5
	NON-DOC	11	-9.52941	3.93887	-10	3	-15	0

Abbreviations: GRP: group; Ndiffval: number of different values; SD: standard-deviation; IQR: interquartile range

Table 11: *Boxplots of the DRS distribution*



The Rancho Los Amigos Levels of Cognitive Functioning (LCF)

At admission, the scores' distribution was significantly different between the 3 categories (Student's t-test, p-value<0.001 for each comparison). The NON-DOC patients globally received the higher scores with a mean of 4.71 ± 0.99 when compared to the CMD patients (3.21±1.04) and the DOC ones (2±0.48).

A significant difference persisted at discharge, with a mean of 7.12 ± 1.73 for the NON-

DOC patients, 6.06±1.87 for the CDM patients and 2.58±1.08 for the DOC patients (Student's t-test: CMD vs. DOC, p-value<0.001; CDM vs. NON-DOC, p-value=0.03; DOC vs. NON-DOC, p-value<0.001).

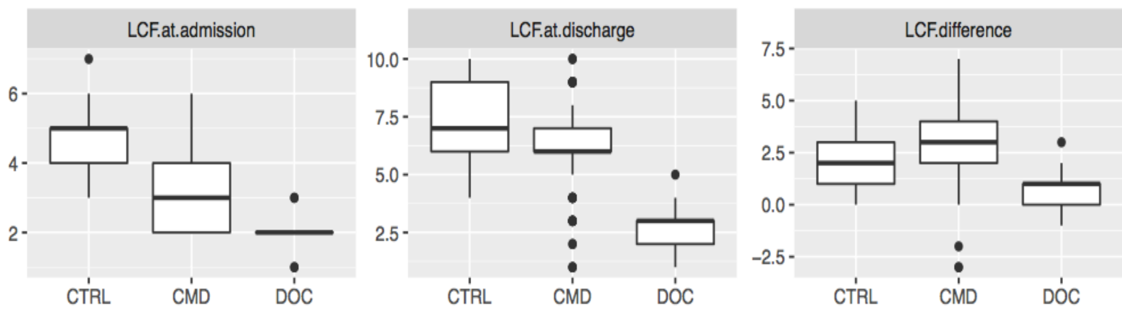
The difference between the scores at admission and discharge were significantly greater for the CMD (2.85±1.79) and the NON-DOC (2.42 ± 1.38) patients than for the DOC patients (0.58±0.97), with a p-value<0.001 according to Student's t-test for both comparisons. No significant difference was found between the CMD and NON-DOC categories (Student's t-test, p-value=0.256).

Table 11: *Detailed LCF distribution*

Variable	GRP	Ndiffval	Mean	SD	Median	IQR	Min	Max
LCF at admission	CMD	5	3.20952	1.05334	3	2	2	6
	DOC	3	2	0.4714	2	0	1	3
	NON-DOC	5	4.70588	0.98518	5	1	3	7
LCF at discharge	CMD	10	6.05714	1.85963	6	1	1	10
	DOC	5	2.57895	1.07061	3	1	1	5
	NON-DOC	7	7.11765	1.7278	7	3	4	10
LCF difference	CMD	10	2.84762	1.78013	3	2	-3	7
	DOC	5	0.57895	0.96124	1	1	-1	3
	NON-DOC	6	2.41176	1.37199	2	2	0	5

Abbreviations: GRP: group; Ndiffval: number of different values; SD: standard-deviation; IQR: interquartile range

Table 12: *Boxplots of the LCF distribution*



The modified Rankin Scale (mRS)

At admission, the mRS took only two different values: 6 (5.71%) of the CMD patients and 4 (23.53%) of the NON-DOC patients received a score of 4, whereas 99 (94.29%) of the

CMD patients, all of the DOC patients (100%) and 13 (76.47%) of the NON-DOC patients received a score of 5. Fischer's exact test for differences in distribution between the CMD and the DOC patients was not significant (p-value=0.589). Lower scores were observed for the NON-DOC category than for the CMD and DOC ones and Fischer's exact test for differences in distribution was significant (NON-DOC vs. CMD, p-value=0.033; NON-DOC vs. DOC, p-value=0.004).

CMD and NON-DOC patients received at discharge a significantly better score (3.78±1.01 and 3.53±1.13) than the DOC patients (4.85±0.51), with a p-value<0.001 in both comparisons (Student's t-test). The scoring of the CMD and the NON-DOC patients was not significantly different (Student's t-test, p-value=0.413).

The CMD and NON-DOC patients also showed a significantly better improving than the DOC ones, with a difference of -1.18±0.96 and -1.24±0.98 versus -0.16±0.51 in the DOC category (Student's t-test, p-value<0.001 for both comparisons). Again, no significant difference was found between the CMD and NON-DOC categories (Student's t-test, p-value=0.803).

Table 13: *Summary of the mRS results at admission*

Variable	Value	CMD n.	DOC n.	NON-DOC n.	CMD prop.	DOC prop.	NON-DOC prop.
mRS at admission	4	6	0	4	0.05714	0	0.23529
	5	99	19	13	0.94286	1	0.76471

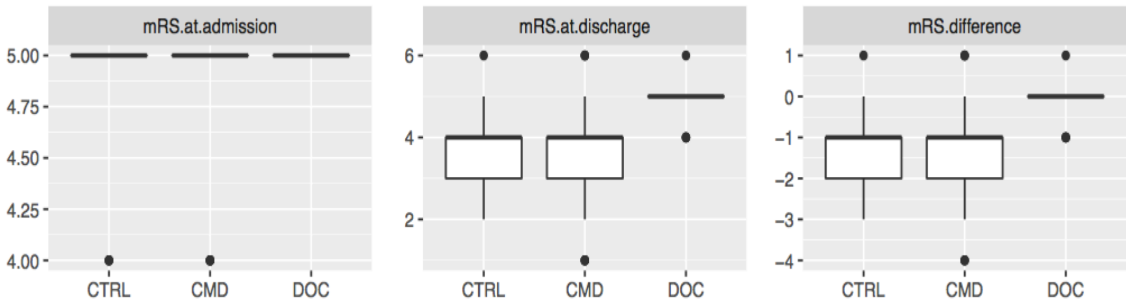
Abbreviations: n: number; prop: proportion

Table 14: *Detailed mRS distribution*

Variable	GRP	Ndiffval	Mean	SD	Median	IQR	Min	Max
mRS at discharge	CMD	6	3.77143	1.00247	4	1	1	6
	DOC	3	4.84211	0.50146	5	0	4	6
	NON-DOC	5	3.52941	1.12459	4	1	2	6
mRS difference	CMD	6	-1.17143	0.95532	-1	1	-4	1
	DOC	3	-0.15789	0.50146	0	0	-1	1
	NON-DOC	5	-1.23529	0.97014	-1	1	-3	1

Abbreviations: GRP: group; Ndiffval: number of different values; SD: standard-deviation; IQR: interquartile range

Table 15: *Boxplots of the mRS distribution*



The Functional Ambulation Classification Scale (FAC)

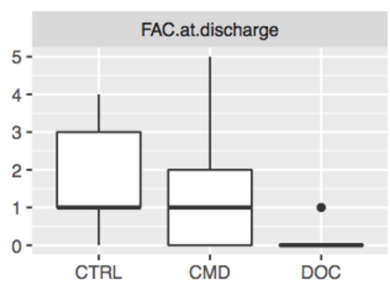
CMD and NON-DOC patients had a significantly better score at discharge (1.30±1.38 and 1.65±1.37) when compared to the DOC patients (0.06±0.23), with a p-value<0.001 for both comparisons (Student's t-test), but no significant difference between the CDM and NON-DOC patients was found (Student's t-test, p-value=0.336).

Table 16: *Detailed FAC distribution*

Variable	GRP	Ndiffval	Mean	SD	Median	IQR	Min	Max
FAC at discharge	CMD	6	1.29524	1.37927	1	2	0	5
	DOC	2	0.05263	0.22942	0	0	0	1
	NON-DOC	5	1.64706	1.36662	1	2	0	4

Abbreviations: GRP: group; Ndiffval: number of different values; SD: standard-deviation; IQR: interquartile range

Table 17: *Boxplots for the FAC distribution*



Consciousness recovery

According to the CRS-R, 75 of the CMD patients (71.43%) and 1 of DOC patient (5.26%) presented a potential of consciousness recovery, whereas 30 of the CMD (28.57%) and 18 of the DOC patients (94.74%) did not.

The sensibility and specificity were estimated at 71.43% (97.5% CI: 62.15-79.19%) and 94.74% (97.5% CI: 75.36-99.06%) respectively.

The positive predictive value was estimated at 98.68 % (97.5% CI: 92.92-99.77%) and the negative predictive value at 37.50% (97.5% CI: 25.21-51.64%).

Table 18: *Summary of the sensibility and specificity of the prediction of consciousness recovery according to the CRS-R.*

	Estimation	2.5 %	97.5 %
Accuracy	0.7500000	0.6670521	0.8179236
Sensitivity	0.7142857	0.6215166	0.7919288
Specificity	0.9473684	0.7536127	0.9906480
Positive predictive value	0.9868421	0.9291633	0.9976735
Negative predictive value	0.3750000	0.2521527	0.5163724

DISCUSSION

In our study, we can overall see that CMD patients are associated with better functional outcomes than the patients suffering from DOC and furthermore, seem to have very similar outcomes to the NON-DOC patients.

At admission, three of the outcome scales (ERBI, DRS and LCF) are already able to highlight a significant difference between the three categories. The NON-DOC patients received the better scores. The CMD patients received intermediate scores, less favourable than the NON-DOC patients, but significantly better than the DOC ones. This confirms the fact that patients with covert consciousness can already be detected in the acute phase. Indeed, Edlow *and al*. (31) revealed that fMRI and EEG could detect command-following and higher-order cortical function in patients suffering from acute brain injuries, in ICU settings. Likewise, Pincherle *and al.* (55) demonstrated the ability of the MBT-r to clinically identify patients with residual cognition in the early stage after a brain injury. Furthermore, Braiman *and al.* (67) investigated the EEG response latencies to natural speech envelope and were able to identify a subgroup of acute severely brain-injured patients capable of fMRI mentally imagery tasks and whose EEG response latencies were undistinguishable from those in healthy subjects. The GOS and the mRS prove to be not adequate to detect any significant difference between respectively the CMD and NON-DOC patients or the CMD and DOC patients. Although the GOS is widely used and recognized for outcome measures, it has been criticised for its lack of sensitivity (68). Some reservations concerning its reliability were also expressed by Lu *and al*. (69) who investigated the impact of misclassifications in clinical trials. In a systematic review from Quinn *and al*. (64), the reliability of the mRS remained subject to uncertainties with potentially important inter-observer variability.

At discharge, the GOS, ERBI, mRS and FAC show significant differences between the CMD and DOC patients, but CMD and NON-DOC patients don't seem to significantly differ. Those findings reinforce the importance of detecting CMD patients as, even though they are often wrongly diagnosed as DOC, their outcome seems to be closer to the NON-DOC patients that the DOC ones. The DRS and LCF can still highlight a significant difference between the three categories, the CMD patients showing a better functional recovery than the DOC patients, but less favourable than the NON-DOC patients. Those two scales have been designed not only to assess patients emerging from coma but also throughout their recovery and reinsertion into community (62-63). Unlike the other scales, the DRS design allows the scoring and recognition of cognitive capacities independently from motor abilities. It also contains items in regard of the level of functioning, from not only the physical aspect, but also through mental, emotional and social perspective. For its part, the LCF allows the investigation of neuropsychological aspects absent from the other scales' scoring, such as memory, learning capacities and ability to experience and recognise feelings. The fact that those two scales investigate in a more complex and detailed manner the different aspects sustaining recovery may provide an explanation for their higher sensitivity to assess subtle differences in patients with outcomes already considered as good. Indeed, when looking at the distribution of the outcome scores, the CMD and NON-DOC patients are more likely to reach values considered as "good outcome" than the DOC patients. In fact, all the DOC patients received at discharge a score considered as "poor outcome" when assessed with the GOS, LCF and FAC. Although CMD patients are more likely to have good outcomes, it is important to remember that not all of them will. The highlighting of covert consciousness doesn't assure a good outcome. Indeed, CMD patients may have preserved cognitive capacities but still remain unable to verbally or behaviourally express it, therefore preventing them to progress and reach good recovery. The inability to express those preserved cognitive capacities can be due to permanent impairments in efferent pathways but can also be correlated to the multidimensional character of consciousness (70). Indeed, the preserved cognition in CMD patients represents only one dimension of those patients' consciousness. The other dimensions, such as the level of arousal, contribute and bring heterogeneity to their global functional outcome. For example, within the CMD category, the DRS scores go from 1 to 29, meaning from patients with complete independence with only a limitation in employment, to patients completely dependant with no communication nor motor ability and no eyes opening, even to painful stimulation.

The fact that CMD patients have better outcomes at discharge than the DOC patients can partly be due to their higher scores at admission, but they also benefit from a significantly better improving of their scores during their hospitalization, as shown with four of the outcome scales (ERBI, DRS, LCF and mRS). Furthermore, the potential of improvement of their scores during their stay is very similar to the NON-DOC patients, as no significant difference can be seen when comparing those two categories. The presence of preserved cognition in CMD patients is an indicator of preserved high-processing integration. This indicates that such patients have better connected brain networks than the DOC patients and therefore more resources to mobilise and commit, which could explain their better potential of improvement. Another explanation could be motivational. Indeed, the presence of conscious awareness in CMD patients may allow them to wilfully improve their recovery, as motivation is thought to play an important part in rehabilitation (71-72). Because they seem to have a better potential of improvement, CMD patients should be identified in order to benefit from the most appropriate care/rehabilitation as they may retain recruitable capacities to reengage with their environment (32), in the acute phase as well as the chronic one. Indeed, Dinkel *and al.* (73) documented significant and durable changes in the white matter microarchitecture up to 2 years post traumatic brain injury. The scores' difference between admission and discharge does give us information about the amount of the patients' progress, but this information should be taken carefully, as it should also be adjusted to the length of hospitalization in order to avoid any misinterpretation. Indeed, the length of stay varied from 7 to 77 days in the CMD category, from 8 to 41 days in the DOC one and from 7 to 46 days in the DOC category.

The choice of the different outcome scales used in our study was based on the fact that each of them brought a different perspective to the results. Indeed, their scoring items differ, which allows a broader view of the different aspects influencing functional outcomes. For example, the FAC is the only scale assessing the walking capacity, which gives precious information on the functional independence. The ERBI details the daily activities, informing on the patient's personal autonomy. The DRS allows the assessment of cognitive capacities independently from the motor abilities, an important aspect when not wanting to underestimate cognition in patients with motor impairments. The LCF investigates neuropsychological aspects such as memory, learning, planning, attention, etc., which gives an impression on how the patient will be able to function in his environment. The GOS and mRS are simple and give a global idea of the patient's degree of disability. However, because of their simplicity, they can score patients with very different abilities the same. For example, two of the CMD patients both received at discharge a GOS score of 3, categorizing them as "severely disabled", but when looking at the other outcome scales' results, those two patients seem to have very different functional outcomes. Indeed, the first one received a LCF score of 8, meaning that the patient was oriented, able to respond appropriately to her environment and to initiate and carry out familiar routines with stand-by assistance, whereas the second one received a LCF score of 3, defined by localized responses to sensory or noxious stimuli, inconsistent responses to simple commands and a need for total assistance. The joint use of the different scales allows therefore a better appreciation of the cognitive and functional capacities of the patients.

The care management of CMD patients raises ethical concerns. Indeed, preserved cognition has been highlighted in those patients, but the meaning and the extent of those patients' needs and capabilities are still to be discovered. For example, the prevention of suffering is crucial, especially with such vulnerable patients, as they might not be able to express their distress. As Fins *and al.* (74) stressed, when faced with uncertainty, universal pain precaution should be the norm. Furthermore, once a certain degree of preserved cognition is highlighted in patients, it becomes an ethical duty to try to restore communication (75). Although the use of fMRI successfully allowed Monti *and al.* (11) to establish communication with a severely brain-injured patient, Bardin *and al.* (76) highlighted the challenges associated with the reliable and consistent use of such method. Notably, they demonstrated that the ability to communicate couldn't necessarily be translated with fMRI. Indeed, two patients enrolled in their study had reliable behavioural ability to communicate but weren't able to perform the fMRI task. Characterization of EEG signals may serve as another potential way to restore communication. In their study, Curley *and al.* (77) demonstrated a global physiological integrity with a preservation of relatively normal EEG background in CMD patients. Although these EEG signals were subject to variations due to arousal fluctuations, their similarity to those in healthy subjects could attest for the ability to communicate and allow the development and use of brain-computer interfaces. Even if the possibility of restored communication with CMD patients hasn't been fully demonstrated yet, it should be pursued, not only in the acute phase, but throughout the recovery, as structural and functional reorganization of cross-hemispheric connections and brain areas associated with language could occur over a long period of time, indicating a late recovery of communication (78).

So far, it doesn't exist a consensus on how to detect and diagnose CMD patients. The CRS-R is used as a gold standard to assess patients suffering from disorders of consciousness, but it still encounters a high rate of misdiagnosis (47). The multiplication of CRS-R assessments during the day has been proposed in order to minimize the risk of misclassification due to the patients' fluctuant states (79). Wannez *and al.* (80) suggested performing at least 5 assessments in order to obtain an accurate diagnosis. However, even after exhaustive behavioural assessments, undetected consciousness can still be highlighted using fMRI, EEG command-following paradigms or EEG responses to transcranial magnetic stimulation (30-81-82). In our study, we investigated the sensitivity and specificity of the prediction of consciousness recovery according to the CRS-R. It proved to be more specific than sensitive, with a low negative predictive value. This implies that the potential of consciousness recovery of certain CMD patients won't be recognised by the CRS-R. For example, one CMD patient was considered having no conscious recovery according to the CRS-R, but her LCF score at discharge was 6 (a score considered as a good outcome). This indicates that, although still needing assistance, she was notably able to follow simple directions, was starting to recognise the staff, to show emerging awareness of self and family, express her discomfort and carry over relearned tasks, which clearly contradicts the CRS-R consciousness recovery prediction. Overall, this reinforces the fact that the CRS-R used alone isn't adapted to consistently detect CMD patients and document an "observable recovery" of their consciousness.

Because it is now recognised that CMD patients demonstrate higher preserved cognition than DOC patients, it is essential to offer them the right to be acknowledged as such by using reliable diagnostic methods. The challenge will be to determine how to manage/associate the use of the current behavioural and functional diagnostic tools available (MBT-r, EEG, fIRM, PET) in order to obtain a standardized accurate diagnosis. Once recognised, CMD patients will be able to consistently benefit from adapted care/rehabilitation to enhance their potential of improvement. Indeed, as discussed above, they prove to have better outcomes than the DOC patients, with higher chances to reach good functional recovery. This will also be achieved through a better understanding of the underlying physiopathology of such condition. In their study, Forgacs *and al.* (83) demonstrated preserved cortical metabolism and normal wake and sleep brain networks' physiology in DOC patients showing fMRI evidence of command following. Similar findings were reported by Stender *and al.* (84). Although those studies give us primordial information, there is still a need for a global physiological model that could be correlated with the different degrees of preserved cognitive capacities. Furthermore, recent studies have expressed the need of an improvement of the DOC taxonomy. Indeed, Bayne *and al*. (85) pointed that the current DOC taxonomy is only based on behavioural criteria, therefore not accounting for the underlying conscious capacities not expressed behaviourally. One of their propositions of improvement would be to revise the diagnostic criteria, by complementing them with brain-based criteria (based on EEG and functional neuroimaging). Similar concerns were addressed by Naccache (4), who proposed a new classification based on behavioural and functional neuroimaging data. Further work will be needed to reach a consensus on how to improve/reform DOC taxonomy.

Limitations

In our study, we compared the different outcomes of CMD patients with the DOC and NON-DOC ones. Because we performed univariate analysis, we didn't take into account the different factors that may have played a role in the patients' outcomes. For example, Cruse *and al.* (86) identified that covert consciousness was more likely to be found in patients suffering from a traumatic brain injury than a non-traumatic one. As the aetiology of the brain injury can have an impact on the diagnosis, it could as well influence the outcome, independently from the diagnosis. Further multivariate analyses are currently ongoing in the Acute Neurorehabilitation Unit (CHUV, Lausanne) and the results will be the subject of a following paper.

Many other confounding factors, such as demographic information (gender, age, etc.) or localisation/extent of the brain injury, could possibly have brought a bias into the results. We enrolled patients that were transferred into the NRA unit, meaning that they were already considered as having a certain potential of rehabilitation, which could have induce a bias of selection. The results should also be taken with caution, as the number of participants in the DOC category (n=19) and the NON-DOC category (n=17) was relatively low.

Another potential source of bias lies in the outcome scales. Indeed, their scoring results from the appreciation and interpretation of the operator, which can be subject to some variability.

Therefore, further multivariate and multicentre studies should be conducted in order to confirm these results.

CONCLUSION

Our study shows that the patients suffering from CMD present overall better functional outcomes than the ones with DOC. The CMD patients also prove to be very similar to the NON-DOC patients in terms of potential of improvement and functional outcomes at discharge.

The ERBI, DRS and LCF demonstrated to be sensitive enough to already distinguish the three groups of patients at admission. They should be used at admission, discharge and throughout the recovery in order to track the patients' progress. Indeed, the fact that they investigate the daily activities, neuropsychological aspects and cognitive abilities independently from motor functions seems to allow them to better assess the cognitive and functional capacities of the patients. The GOS and mRS are interesting in the fact that they give a global idea of the patients' disability but because of their simplicity, they often classify patients with very different functional outcomes in the same category. The CRS-R, by not taking into account motor limitations or neuropsychological aspects, proves to lack sensitivity in detecting consciousness recovery.

Finally, our findings highlight the fact that CMD patients constitute a separate category of patients with better potential of improvement and functional outcomes than the DOC patients, reinforcing the need for them to be recognised as soon as possible, as it could have a direct impact on patient care and influence life and death decisions.

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